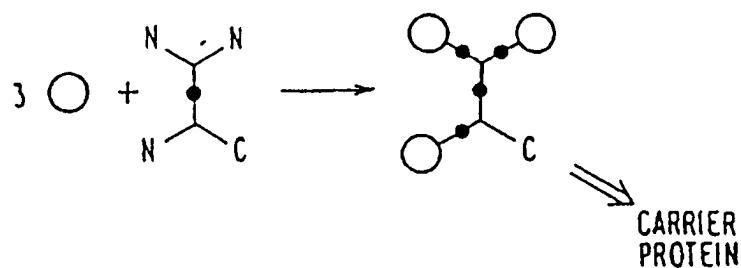


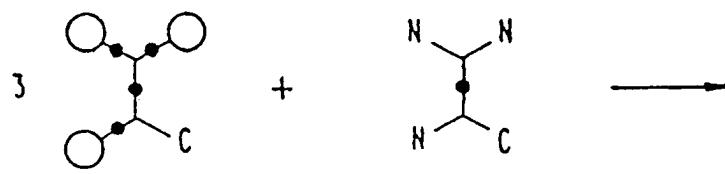


SCHEME I

TRIVALENT CONJUGATE

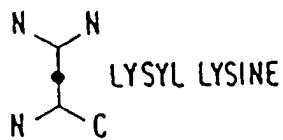


NONAVALENT CONJUGATE



○ Tn -ANTIGEN

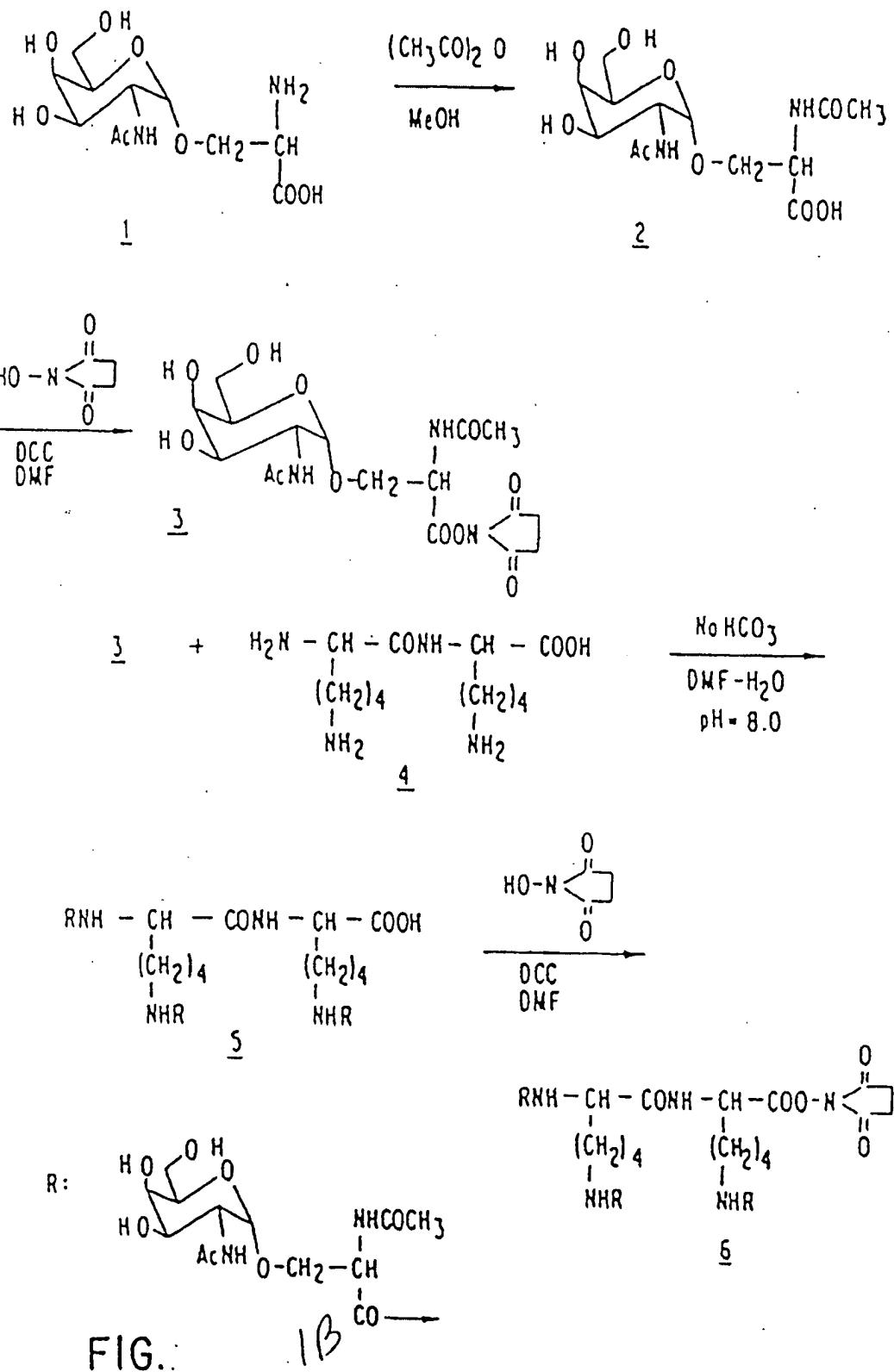
• AMIDE BOND



↔ CARRIER PROTEIN

FIG. 1 A

SCHEME II



SYNTHESIS OF ANTIGEN CLUSTERS.

General formula: $\text{Ac}-(\text{Ser})_m-(\text{Thr})_n-\text{NH}-(\text{CH}_2)_3-\text{COOH}$
 $(m + n \leq 3)$

Examples: $\text{Ac}-\text{Ser}-\text{NH}-(\text{CH}_2)_3-\text{COOH}$ 5
 *

$\text{Ac}-\text{Thr}-\text{NH}-(\text{CH}_2)_3-\text{COOH}$
 *

$\text{Ac}-\text{Ser}-\text{Ser}-\text{NH}-(\text{CH}_2)_3-\text{COOH}$
 * *

$\text{Ac}-\text{Ser}-\text{Ser}-\text{Ser}-\text{NH}-(\text{CH}_2)_3-\text{COOH}$
 * * *

$\text{Ac}-\text{Ser}-\text{Thr}-\text{Thr}-\text{NH}-(\text{CH}_2)_3-\text{COOH}$ 6
 * * *

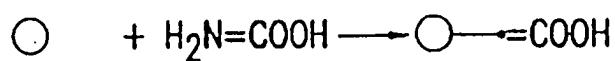
* : GalNAcα1 → / NeuAcα2 → 6GalNAcα1 →

FIG.

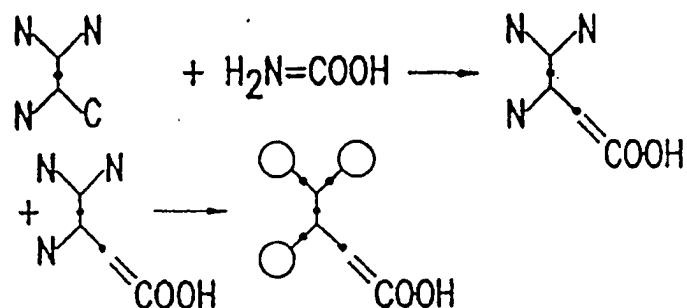
2A

CONSTRUCTION OF MULTIVALENT SYSTEMS.

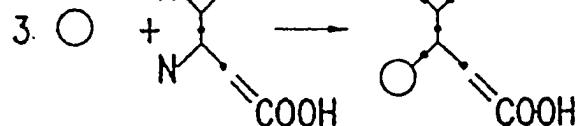
MONOVALENT
CONJUGATE



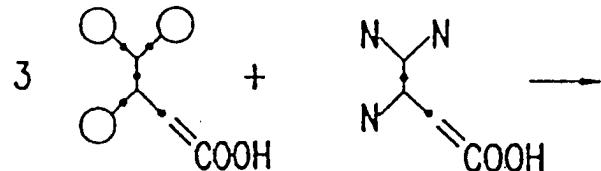
CORE STRUCTURE



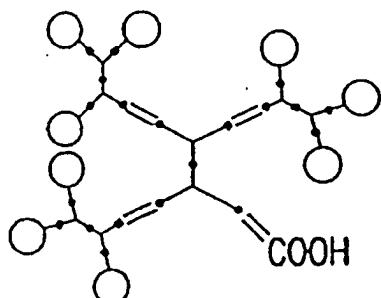
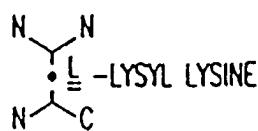
TRIVALENT
CONJUGATE



NONOVALENT
CONJUGATE



$\text{O} (\text{Tn/Sialyl-Tn})_n$
• AMIDE BOND $n=1,2,3,\dots$



$\text{H}_2\text{N}-\text{COOH}$ SPACER ARM (e.g. 4-aminobutyric acid)

FIG.

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DESIGN FOR EFFECTIVE PRESENTATION OF SYNTHETIC ANTIGENS TO IMMUNE SYSTEM.

()_h — carrier protein (e.g. BSA, KLH)

— tripalmitoyl-S-glycerylcysteinyl-seryl-serine

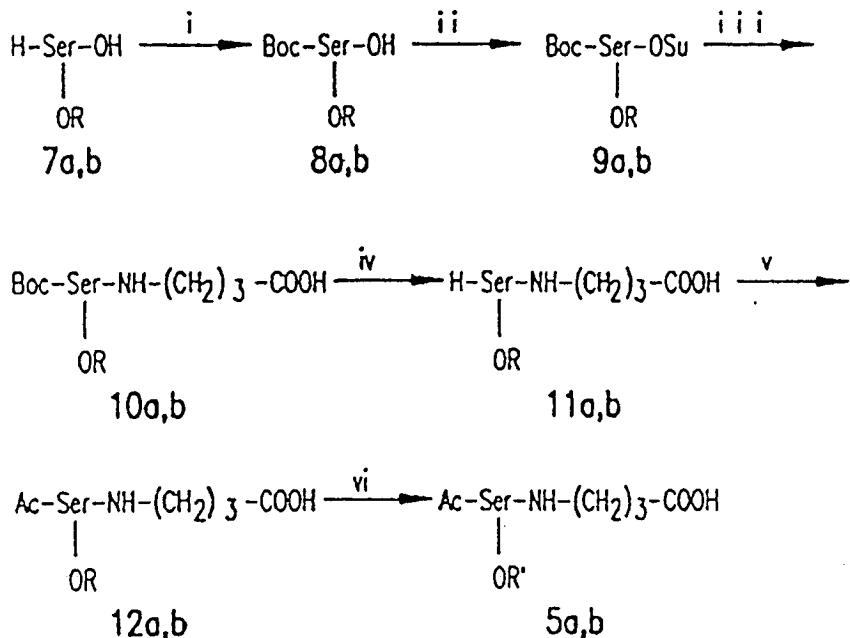
— monophosphoryl lipid A

: constructed antigen systems

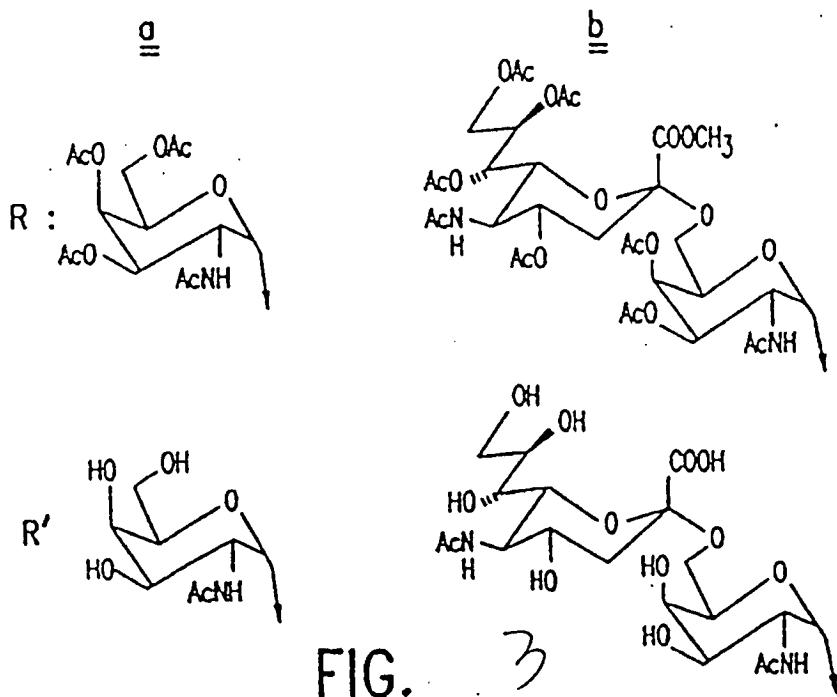
FIG.

26

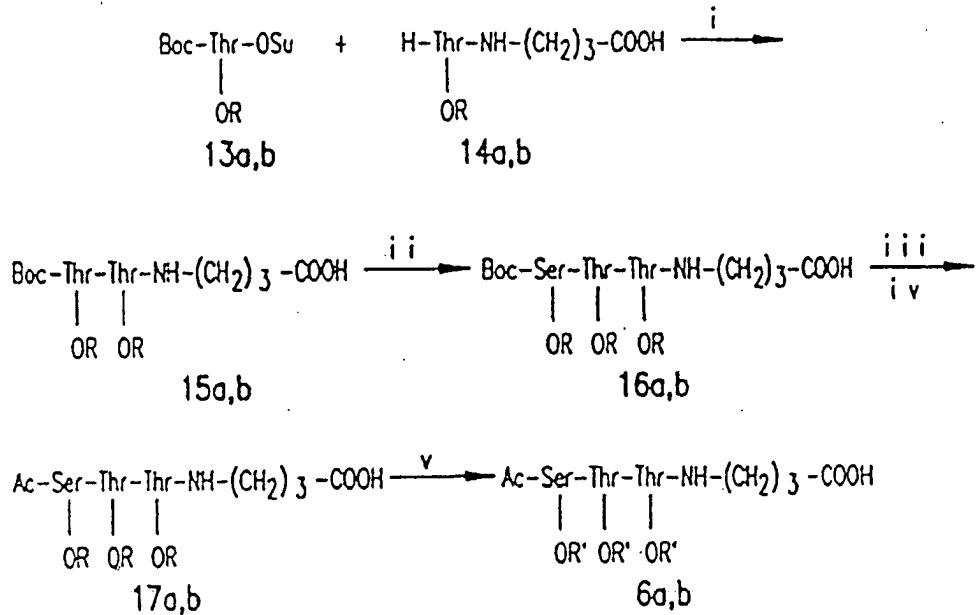
SYNTHESIS OF 5



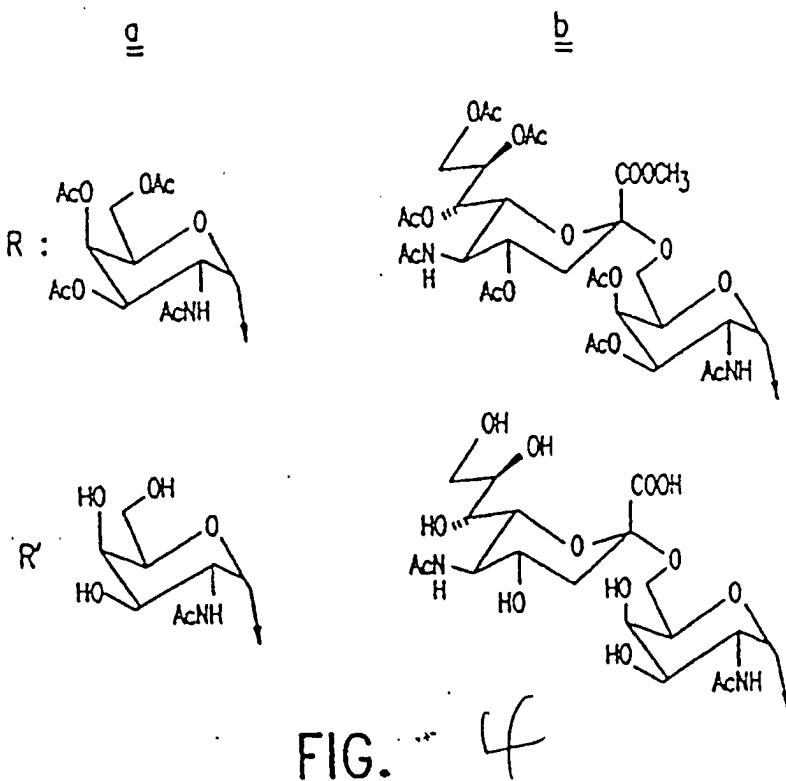
Reagents: i) Boc_2O , Et_3N , MeOH ; ii) NHS , EDC , CH_2Cl_2 ;
 iii) $\text{H}_2\text{N-(CH}_2)_3\text{-COOH}$, Et_3N , DMF ; iv) HCOOH ; v) Ac_2O , MeOH ;
 vi) 10% 1N NaOH in MeOH , 5 min.



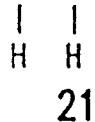
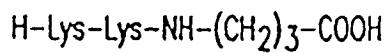
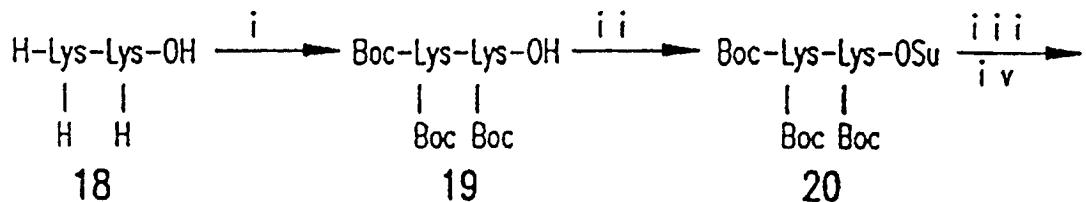
SYNTHESIS OF 6



Reagents: i) Et_3N , DWF; ii) $9\text{a},\text{b}$, Et_3N , DWF; iii) HCOOH ;
 iv) Ac_2O , MeOH; v) 10% 1N NaOH in MeOH, 1 h.

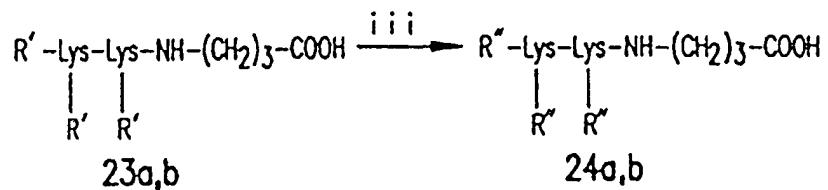
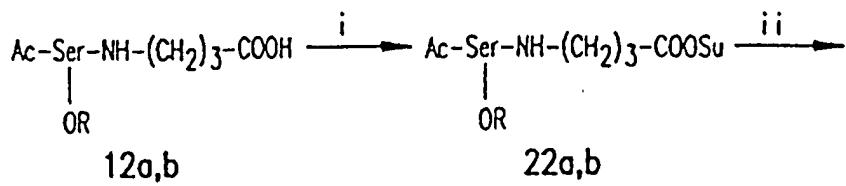


PREPARATION OF CORE STRUCTURE



Reagents: i) Boc_2O , Et_3N , MeOH ; ii) NHS , EDC , CH_2Cl_2 ;
 iii) $\text{H}_2\text{N-(CH}_2)_3\text{-COOH}$, Et_3N , DMF ; iv) HCOOH .

FIG. 2
5X



Reagents: i) NHS, EDC, DMF; ii) 21. Et₃N, DMF-H₂O;
 iii) 10% 1N NaOH in MeOH, 5 min.

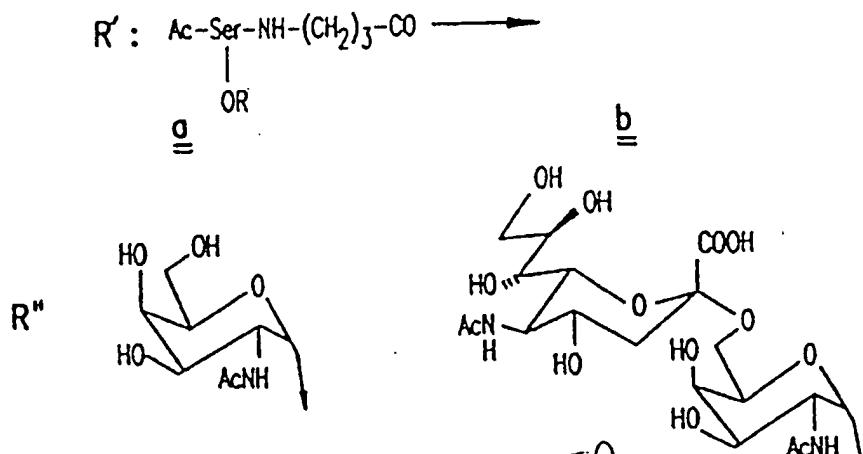
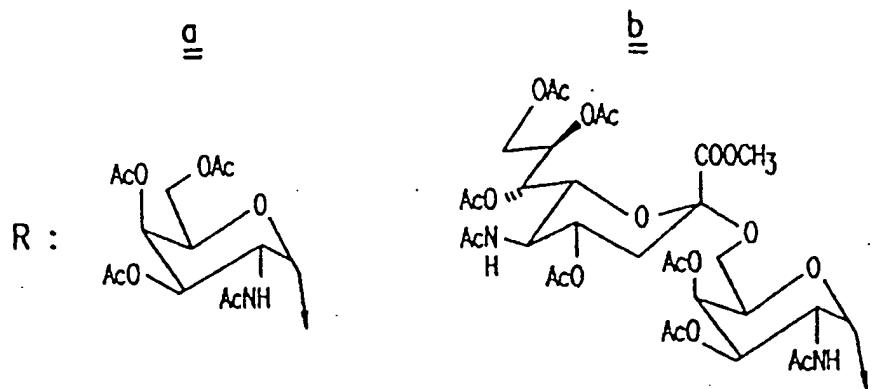
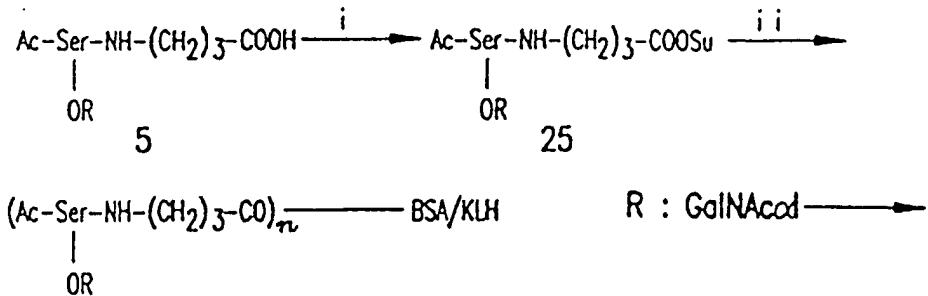


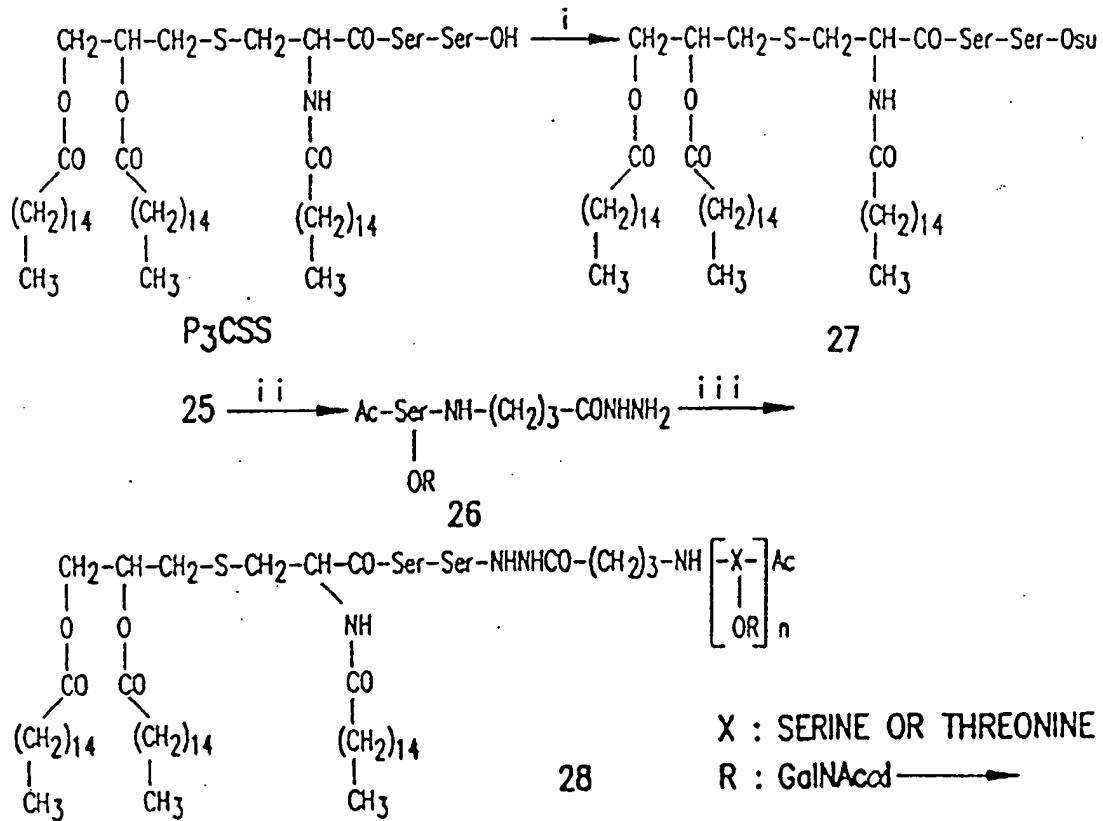
FIG. 5B

CONJUGATION WITH CARRIER PROTEINS



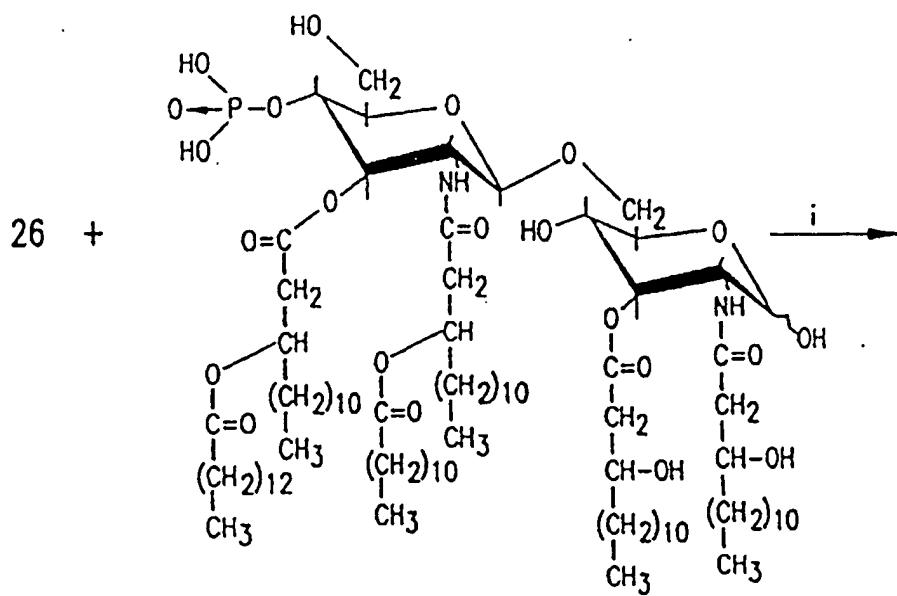
Reagents: i) NHS, EDC, DMF; ii) BSA/KLH, NaHCO₃, DMF-H₂O.

CONJUGATION WITH NON-MACROMOLECULES

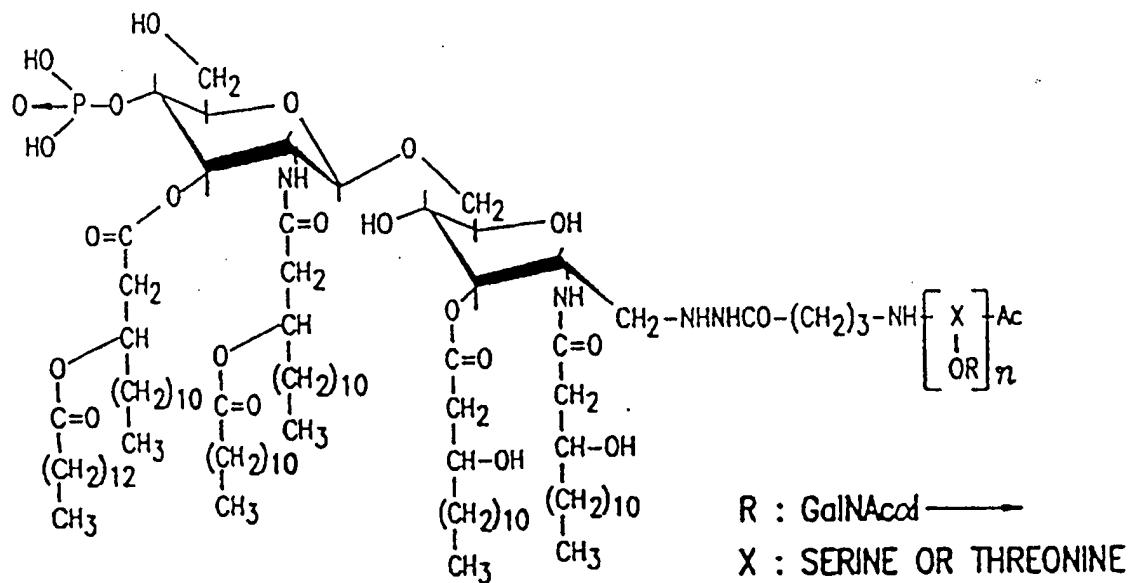


Reagents: i) NHS, EDC, CH_2Cl_2 ; ii) NH_2NH_2 , aq MeOH ; iii) DMF- H_2O .

FIG. - 6A



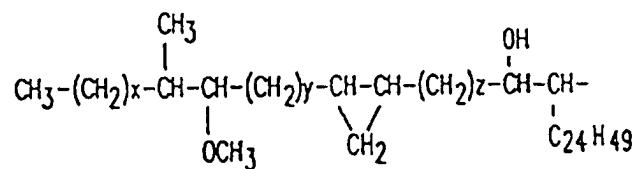
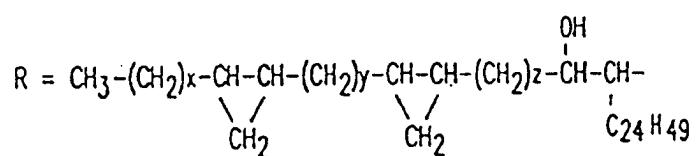
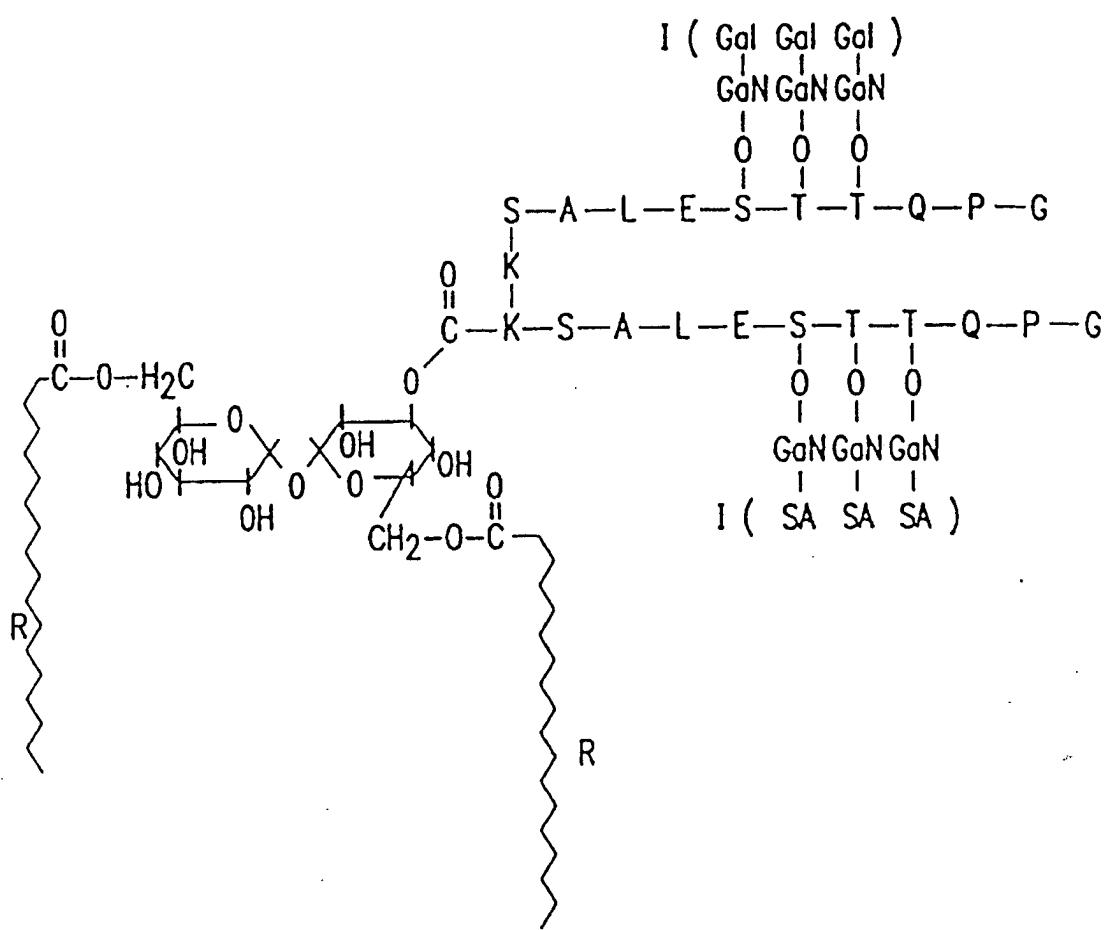
MPL



29

Reagents: i) NaCNBH_3 , NaHCO_3 , H_2O .

FIG. 6B



In general, x,y,z are odd, even and odd number; e.g. 17,14,17

FIG.

2A

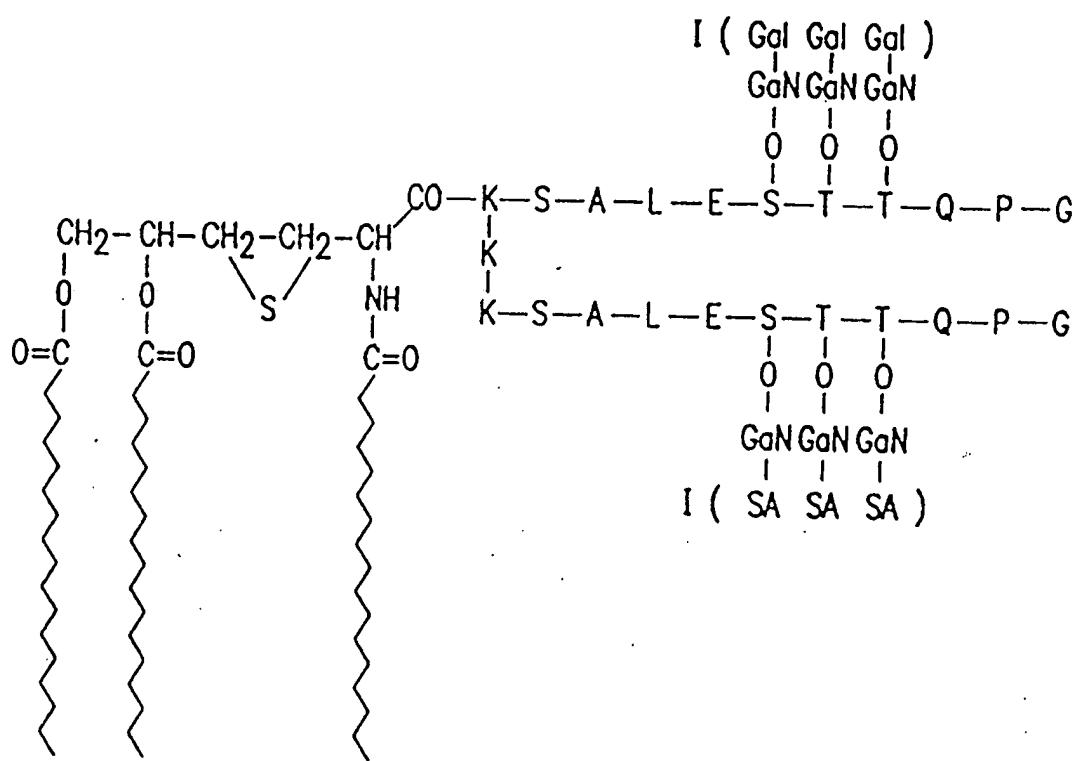
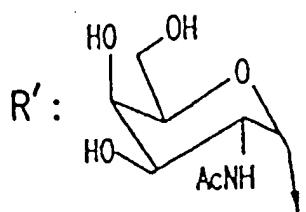
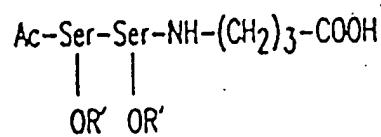
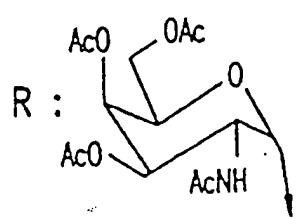
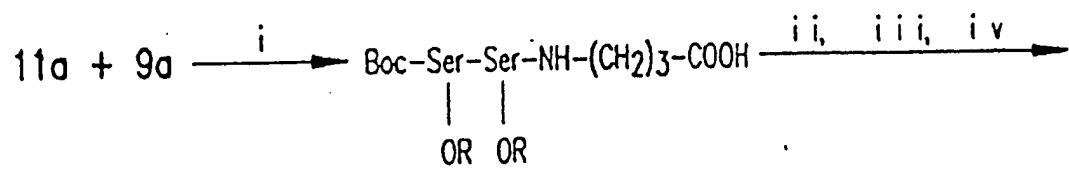


FIG.

7B



Reagents: i) Et₃N, DWF; ii) HCOOH; iii) Ac₂O, MeOH; iv) 10% 1N NaOH-MeOH, 5 min.

FIG. 8

Fig. 9 A

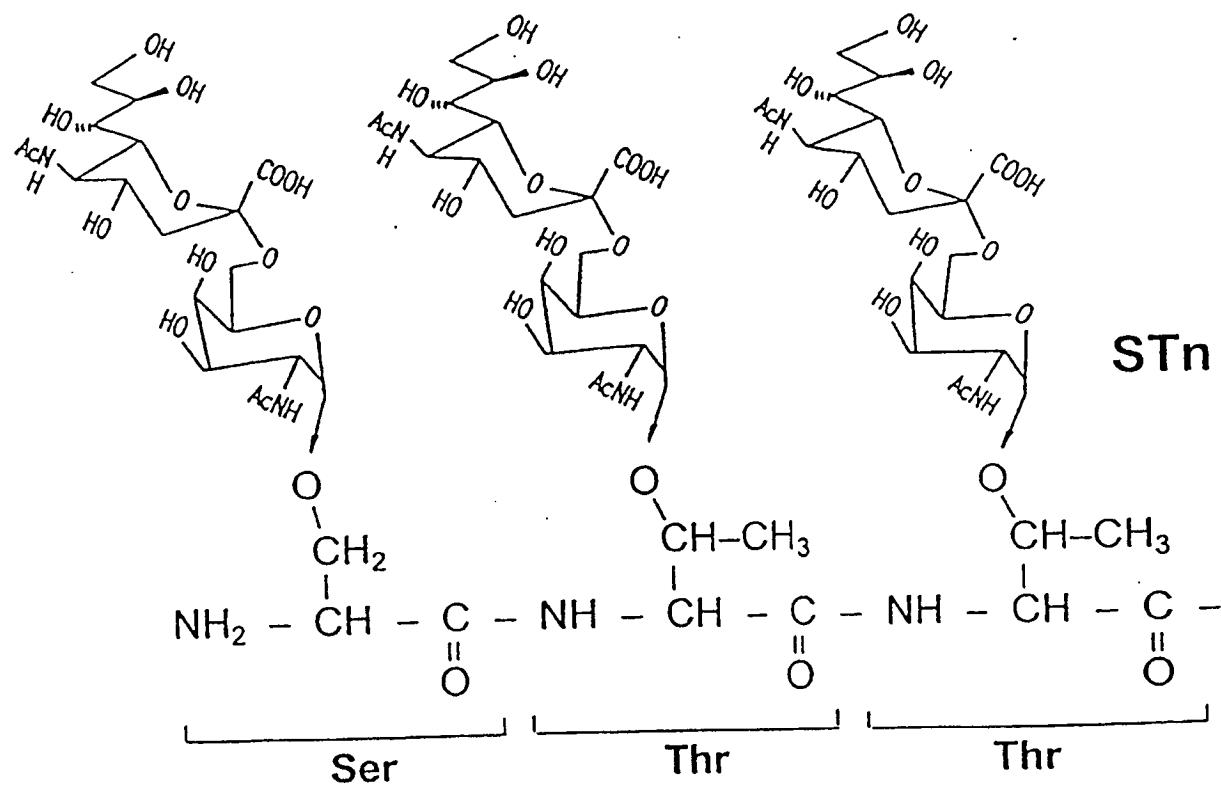
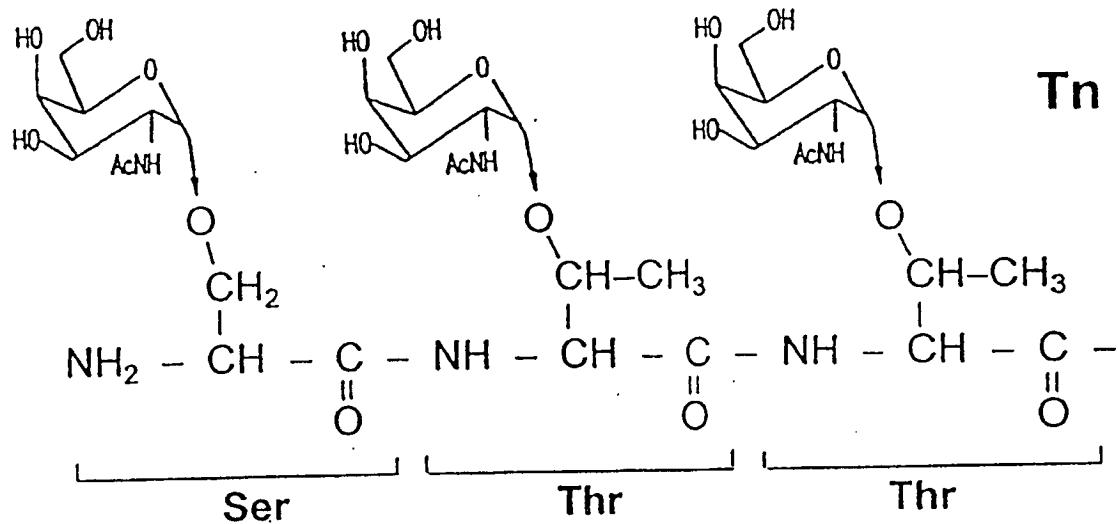
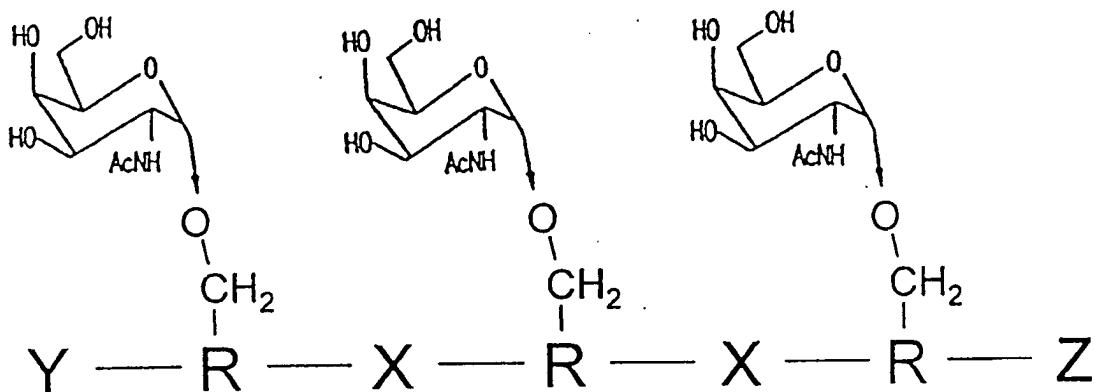


Fig. 9B



Y = terminal protected residue. X = spacer.

Z = active functional group ready to link to core or carrier molecule (e.g. activated carboxyl)

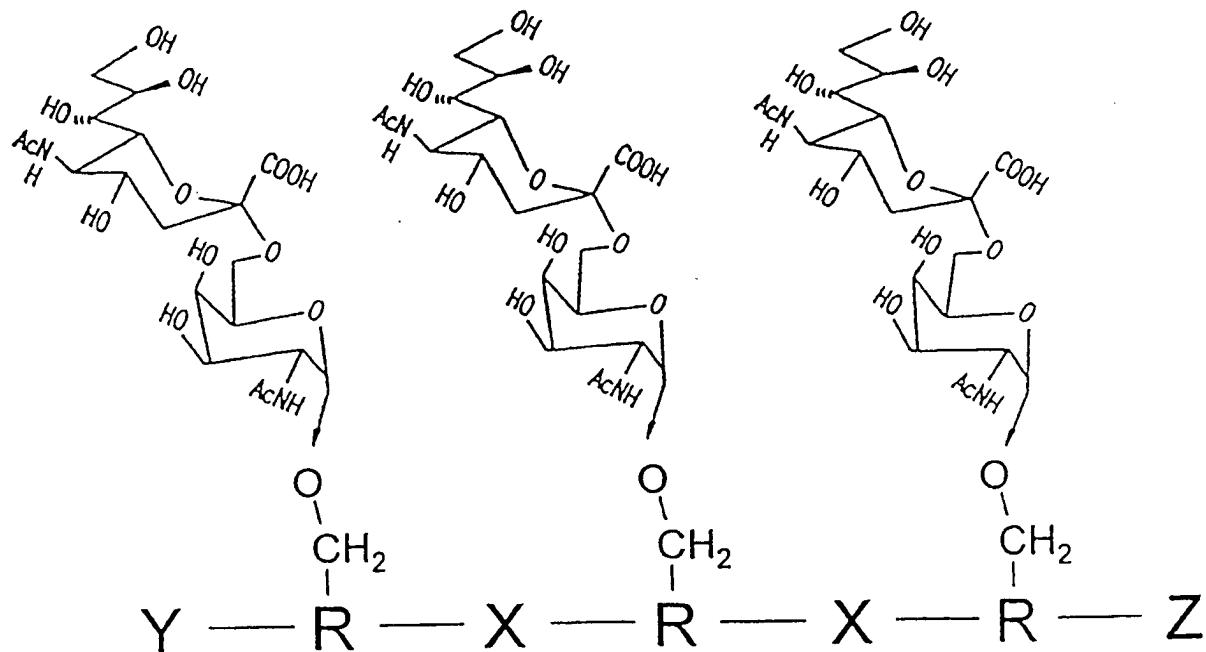


Figure 10

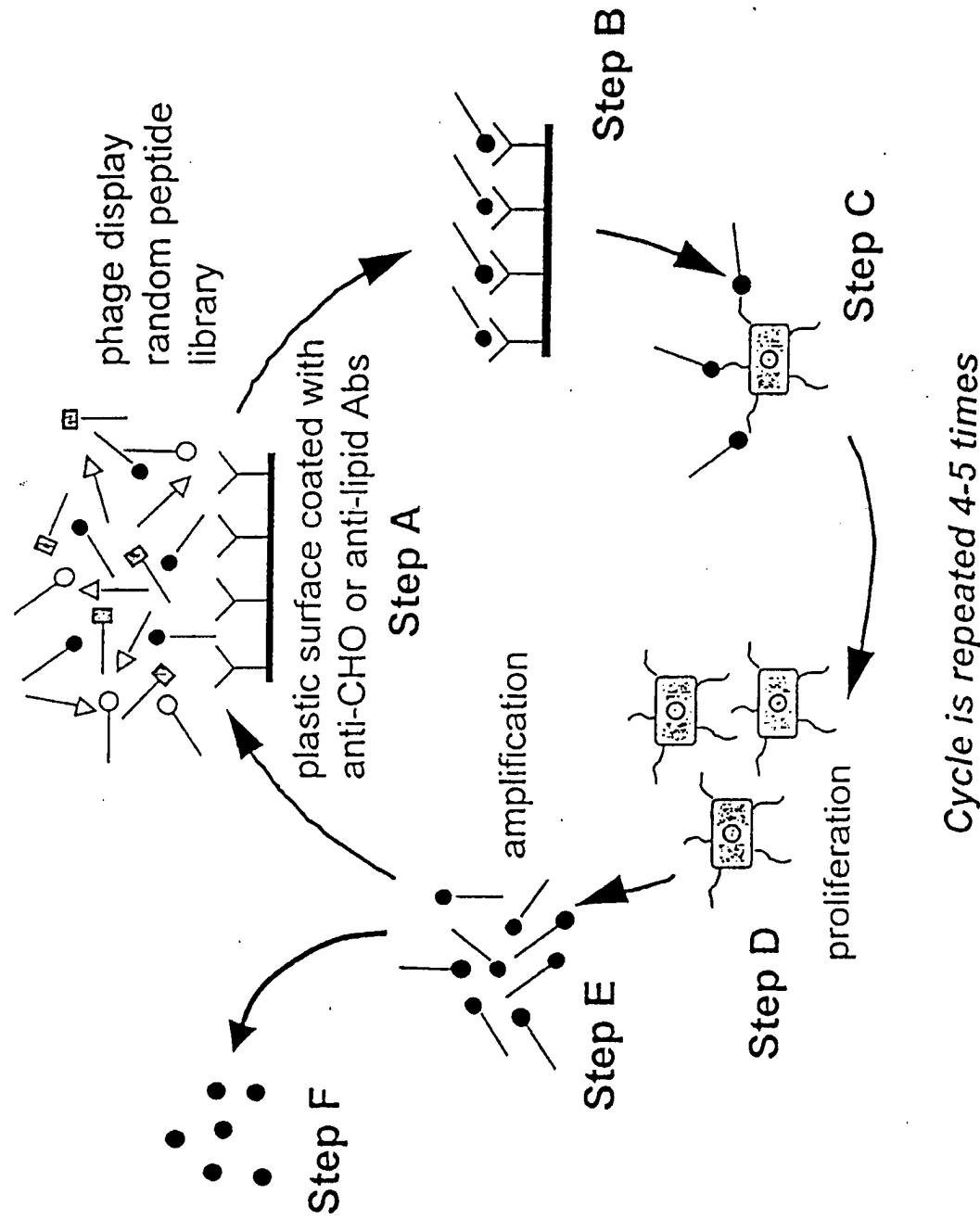


Figure 11A. Class II MHC restricted presentation of extracellular antigen to CD4+ T helper cells.

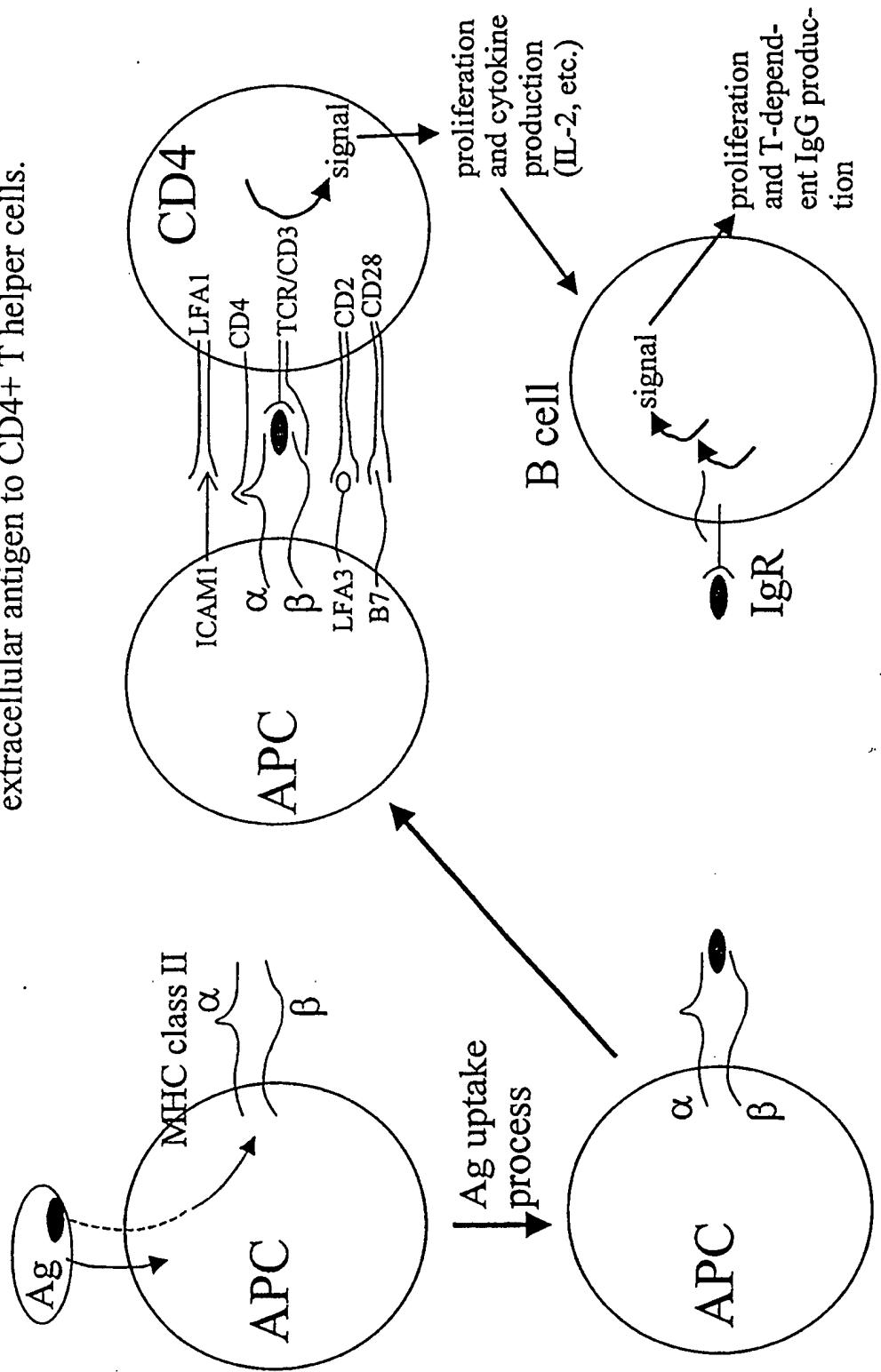


Figure 11B. Class I MHC restricted presentation of endogenously synthesized antigen to CD8+ killer T cells.

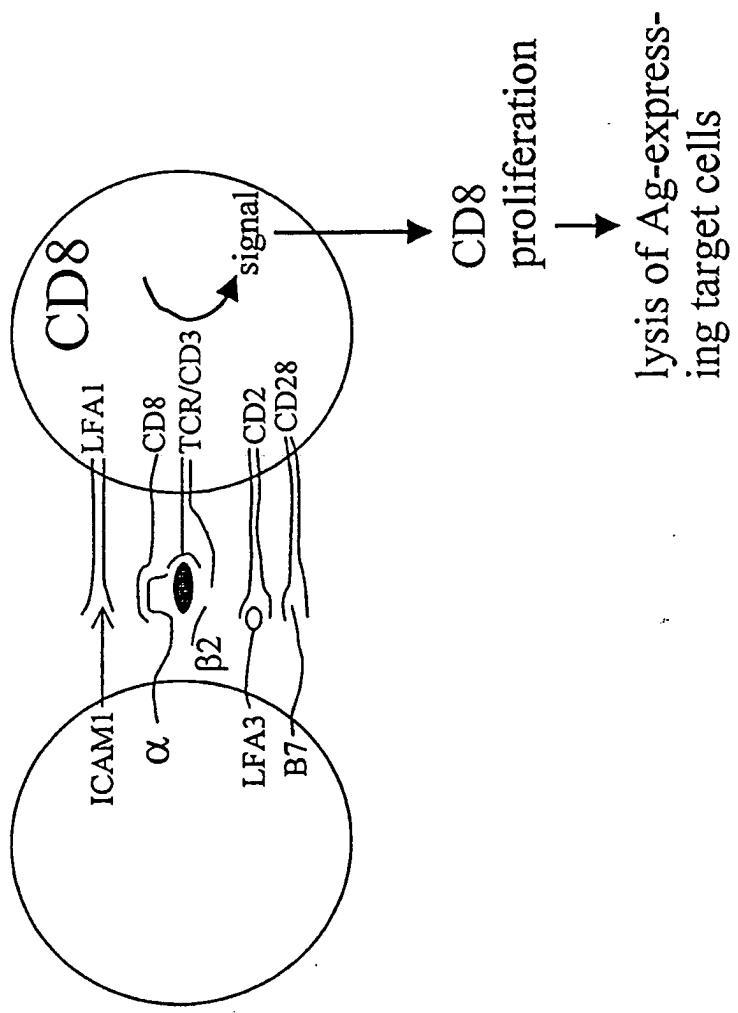


Fig. 12

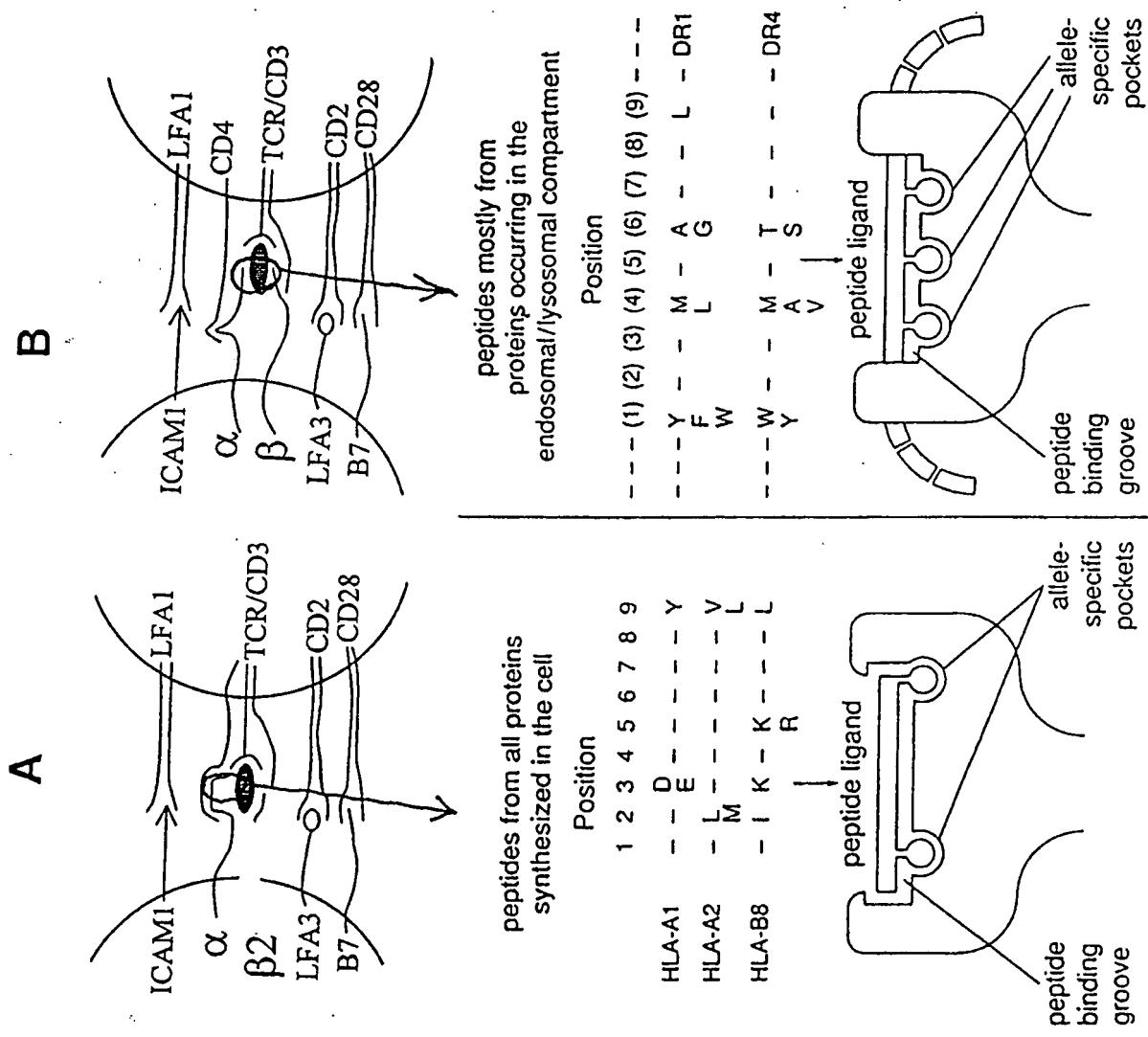


Figure 13

